revoked those opinions under § 310.100 of this chapter.

(b) The 1962 amendments amended section 507 of the act to require the certification, release without certification, or exemption from certification, of all antibiotic drugs on the basis of scientific proof of safety and effectiveness. The amendments provided that FDA implement them for antibiotic drugs that were marketed on April 30, 1963 and were not subject to the certification provisions on that date. FDA is implementing the amendments with respect to antibiotic drugs formerly subject to the new drug provisions of the act through its Drug Efficacy Study Implementation (DESI) program under which the agency is evaluating those antibiotic drugs for efficacy. Until FDA completes that evaluation it will permit continued marketing of those antibiotic drugs under paragraph (c) of this section. The agency is also implementing the 1962 amendments with respect to antibiotic drugs formerly not subject to either the certification or new drug provisions of the act and the agency is evaluating those antibiotic drugs for both safety and efficacy. Until FDA completes that evaluation, it will permit continued marketing of those antibiotic drugs under paragraph (d) of this section.

(c) Unless exempted from certification, FDA will certify or release antibiotic drugs which on April 30, 1963 were the subject of an approved new drug application under section 505 of the act, under regulations providing for certification of the drugs. Although the initial regulation for each of these drugs established under section 507(h) of the act was not conditioned upon an affirmative finding of the effectiveness of the drug, FDA is proceeding under its DESI program to amend or repeal those regulations to provide for certification of those drugs only if they had been shown to be both safe and effective.

(d) Unless exempted from certification, FDA will release without certification an antibiotic drug that was marketed on April 30, 1963, but not subject to certification, and not subject to an approved new drug application on that date, unless FDA has made a determination that the drug has not been shown to be safe or lacks substantial evidence of effectiveness under the DESI program. FDA is proceeding under its DESI program to establish regulations under section 507 to provide for certification of those drugs only if they have been shown to be safe and effective.

[50 FR 7516, Feb. 22, 1985]

PART 431—CERTIFICATION OF ANTIBIOTIC DRUGS

Subpart A—General Provisions

Subpart B—Administrative Procedures

Subpart C—Records and Reports

Subpart D—Confidentiality of Information

AUTHORITY: 21 U.S.C. 351, 352, 353, 355, 357, 379e; 42 U.S.C. 216, 241, 262; 5 U.S.C. 552.

SOURCE: 39 FR 18934, May 30, 1974, unless otherwise noted.

Subpart A—General Provisions

§ 431.1 Requests for certification, check tests and assays, and working standards; information and samples required.

(a) A request for certification of a batch (antibiotic Form 7/Form FDA–1677) is to be addressed to the Food and

Drug Administration, Division of Research and Testing (HFD–470), 200 C St. SW., Washington, DC 20204.

(b) [Reserved]

(c) A person who requests certification or check tests and assays of a batch shall submit with his request the following information and samples:

(1) The batch mark of the drug.

(2) The quantity of each ingredient used in making the batch and a statement that each such ingredient conforms to the requirements or standards prescribed therefor, if any, by specific regulations or official compendium or otherwise approved by the Commissioner.

(3) The size of the batch, including the number of containers of each size in the batch.

(4) The date of the latest assay of the batch.

(5) The results of the latest tests and assays made by or for him on the batch as required for the drug by specific regulations.

(6) The batch mark(s) of the antibiotic(s) used in making the batch.

(7) Unless previously submitted, the results and dates of the latest tests and assays made by or for him on the antibiotic(s) used in making the batch as required by specific regulations.

(8) The number of accurately representative samples that are required for the batch by specific regulations:

(i) In the case of drugs such as dry powders, solutions, ointments, and suspensions, the sample shall be collected by taking single immediate containers, before or after labeling, at such intervals throughout the entire time of packaging the batch that the quantities packaged during the intervals are approximately equal. In no case, however, shall more than 5,000 immediate containers have been packaged during each such interval of sampling, except for a sample collected for sterility testing.

(ii) In the case of drugs in unit dosage forms, such as tablets, capsules, or suppositories, samples shall be collected as follows:

(*a*) From batches exceeding 500,000 units, a representative sample consisting of 100 units shall be collected by taking single units at approximately equal intervals throughout the final production of the batch. If the person packaging the units into dispensing-size containers is not the manufacturer, the representative sample consisting of 100 units shall be collected by taking single units at approximately equal intervals during packaging.

(*b*) From batches of 500,000 units or less, a representative sample consisting of not more than 100 units shall be collected by taking single units at approximately equal intervals throughout the final production of the batch. If the person packaging the units into dispensing-size containers is not the manufacturer, the samples shall be collected by taking single units at approximately equal intervals during packaging. In no case shall more than 5,000 units be produced or packaged during a sampling interval. The minimum acceptable sample size shall be as specified in the appropriate monograph.

(*c*) When the manufacturing process is such that it is not feasible to collect the samples throughout the final production of the batch (e.g., if tablets undergo further processing, such as polishing or coating, after being compressed), the samples may be collected from bulk containers of the finished product, according to the following requirements:

(*1*) For batches exceeding 500,000 units: If the batch is in more than 100 containers, the sample is 1 unit from each container. If the batch is in 100 containers or less, the sample is 100 units, taken in approximately equal amounts from each container.

(*2*) For batches of 500,000 units or less: If the batch is in more than 100 containers, the sample is 1 unit from each container. If the batch is in 100 containers or less, the sample is at least 1 unit for every 5,000 units in the batch taken in approximately equal amounts from each container. The sample shall not be less than the minimum number of units specified in the appropriate monograph.

(iii) In the case of drugs packaged for repacking or for use in the manufacture of another drug, the sample must be representative of the batch. Such samples may be taken from a composite composed of portions taken from a

representative number of bulk containers, the composite consisting of no more than 10 times the amount required for conducting the required tests and assays. Such samples are not required if they have been previously submitted.

(iv) In the case of a sterile drug packaged in combination with containers of a sterile diluent, the sample shall be collected by taking 20 immediate containers of the diluent collected at regular intervals throughout each filling operation, except that if the diluent is sterilized after filling into containers, the representative sample shall consist of 20 immediate containers collected from each sterilizer load and each container shall be taken from a different part of each such sterilizer load. In the case of sterile drugs packaged in combination with sterile dispensers, the sample shall be collected by taking 20 dispensers from each sterilizer load, and each dispenser shall be taken from a different part of such sterilizer load.

(9) In the case of an initial request for certification, each ingredient used in making the batch other than ingredients required by specific regulations: 1 package of each containing approximately 5 grams. Results and dates of the latest tests and assays made by or for him on such ingredients shall precede or accompany the submission.

(10) The results and dates of tests and assays made by or for him on the nonantibiotic active ingredients in the batch.

(11) If such batch or any part thereof is to be packaged with a sterile diluent or sterile dispenser, such request shall also be accompanied by a statement that such diluent or dispenser is sterile and conforms to the requirements prescribed therefor by specific regulations.

(d) Each sample submitted pursuant to the regulations in this chapter shall be addressed to the Commissioner. Its package shall be clearly identified as to its contents and shall bear the name and post-office address of the person submitting it.

(e) In addition to the information and samples specifically required to be submitted to the Commissioner by the regulations in this chapter, the person who requests certification of a batch shall submit such further information and samples as the Commissioner may require for the purpose of investigations to determine whether or not such batch complies with the requirements of § 431.10 for the issuance of a certificate.

(f) Reference standards identical to working standards are available from: U.S.P. Reference Standards, 12601 Twinbrook Parkway, Rockville, Md. 20857, 301–881–0666.

[39 FR 18934, May 30, 1974, as amended at 41 FR 46852, Oct. 26, 1976; 43 FR 41195, 41197, Sept. 15, 1978; 45 FR 40111, June 30, 1980; 50 FR 7516, Feb. 22, 1985; 50 FR 8997, Mar. 6, 1985; 55 FR 11582, Mar. 29, 1990]

§ 431.5 Samples for sterility testing.

(a) *''Filling operation'' and ''sample'' defined.* (1) The term ''filling operation'' when used in connection with samples of a batch required for sterility testing refers to that period of time not longer than 24 consecutive hours during which a homogeneous quantity of drug is being filled continuously into market-size containers and during which no changes are made in the equipment used for filling. (Short rest periods for operators of the filling equipment and the time required to change operators between consecutive shifts are not considered as a break in continuity of the filling operation.) If more than one filling device is used during the filling operation, the samples shall include immediate containers filled by each device, and each such container shall be identified with a mark corresponding to that assigned to the filling device. If more than one filling operation is required to fill a batch, each container in the sample shall be identified with the number of the operation.

(2) For the purpose of sterility testing, the term ''sample'' means the total number of containers taken from each filling operation.

(b) *Packaging requirements for samples.* If a batch of a sterile antibiotic is packaged for repacking or for use as an ingredient in the manufacture of another drug, the sample required for sterility testing may be packaged in one container, in lieu of 20 containers, or in two containers in lieu of 40 containers, under the following conditions: